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REMARKS

Objections to the Disclosure

The Examiner has objected to the use of Internet addresses in the specification at page 18, line 9, and at page 52, line 23. Applicants apologize for these errors and have amended the specification to comply with the Examiner's request.

Applicants respectfully request amendment of the specification at page 40 to insert appropriate SEQ ID NOs. This amendment does not constitute new matter, as all sequence information was included in the application as originally filed; it merely directs the reader more precisely to the appropriate, specific sequences. As provided in MPEP 2163.06, "information contained in any one of the specification, claims or drawings of the application as filed may be added to any other part of the application without introducing new matter." In fact, such cross-reference of sequences described in the specification to those appearing in the sequence listing is *required* under 37 C.F.R. 1.821(d) and is submitted herewith in compliance with such mandate.

In the second amended paragraph of page 40, once the required statement of SEQ ID NO. is made, the correction of 1307 to 1306 is apparent to one of skill in the art, as SEQ ID NO: 16 comprises 1309 nucleotides when the start codon is included. Removal of the terminal "atg" results in the promoter sequence being 1306 nucleotides in length. Thus this does not constitute new matter; as provided in MPEP 2163.07, "An amendment to correct an obvious error does not constitute new matter where one skilled in the art would not only recognize the existence of error in the specification, but also the appropriate correction."

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Objections to the Claims

The Examiner has objected to Claim 15 as reciting a non-elected invention. Claim 15 has been amended to remove reference to any non-elected invention.

The Examiner has suggested amending Claim 18 to provide the proper article. Applicants thank the Examiner for this suggestion and have so amended Claim 18.

Claim Rejections – 35 USC § 112, Second Paragraph

The Examiner has rejected Claims 15-32 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The Examiner states that in claim 15, part (b), it is unclear what is intended by "operable fragments." Dependent claims 16-32 are included in the rejection.

The Applicants traverse this rejection and direct the Examiner's attention to page 21 of the specification, particularly lines 5 through 17. As stated therein, "Smaller fragments may yet contain the regulatory properties of the promoter, and deletion analysis is one method of identifying essential regions." Also, on page 22, the specification provides: "Further, the nucleotide sequence for the promoter of the invention, the *ZmAxig1* promoter, as well as fragments and variants thereof, can be provided in expression cassettes along with heterologous nucleotide sequences for expression in the plant or plant tissue culture of interest." Applicants respectfully assert that the meaning of "operable fragments" of the promoter is clear to one of skill in the art, and the rejection should be withdrawn.

The Examiner states that claim 15, part (e), lacks active, positive steps delimiting how this use is actually practiced.

New Claim 45 comprises the former 15(e) element. The Applicants traverse the rejection and respectfully direct the Examiner's attention to page 30 of the specification, lines 3 through 19, for support of the claim and ad quate explanation

of the steps to be practiced. Further, Applicants respectfully submit that the requirement of Section 112, second paragraph, for "distinctly claiming the subject matter which the applicant regards as his invention" concerns setting the boundaries of the scope of the claim. "*The purpose of claims is not to explain the technology or how it works*, but to state the legal boundaries of the patent grant. A claim is not 'indefinite' simply because it is hard to understand when viewed without benefit of the specification." S3 Inc. v. nVIDIA Corp., 259 F.3d 1364, 59 USPQ2d 1745 (Fed. Cir. 2001) (emphasis added). The Court has also held that "A decision as to whether a claim is invalid under this provision requires a determination whether those skilled in the art would understand what is claimed." Amgen, Inc. v. Chugai Pharmaceutical Co., Ltd., 927 F.2d 1200, 18 USPQ2d 1016 (Fed. Cir. 1991), *cert. denied*, 516 U.S. 988 (1991). Applicants submit that a person of skill in the art would fully understand the content and scope of Claim 45 when read in light of the specification, and ask that the rejection be withdrawn.

The Examiner states that Claim 20 is indefinite for failing to recite a proper Markush group.

The Applicants have amended Claim 20 and ask that the rejection be withdrawn.

The Examiner states that in Claim 21, "disruption of plant fertility" is unclear.

The Applicants have modified Claim 21 to comprise "modification of plant fertility" and ask that the rejection be withdrawn. As described in the specification, in particular in Example 4, restoration of fertility in male-sterile maize plants is a preferred embodiment; however, to one of skill in the art, the tissue-preferred, inducible nature of the isolated promoter suggests additional uses, including others related to plant fertility.

The Examiner states that Claim 32 is indefinite for lacking agreement between the preamble and method steps.

The Applicants have amended Claim 32 and submit that the preamble and method steps are now in proper agreement.

Thus, the Applicants ask that the rejections under 35 USC 112, second paragraph, be withdrawn.

Claim Rejections – 35 USC § 112, First Paragraph, Enablement

The Examiner states that Claims 13 and 21 are rejected under 35 U.S.C. 112, first paragraph, for not reasonably providing enablement for any isolated polynucleotide having at least 75% sequence identity with SEQ ID NO: 16, operable fragments thereof, polynucleotides amplified from *Zea mays* nucleic acids library using specified primers, and nucleic acids from the 5' regulatory region of any polynucleotide having 75% sequence identity to *ZmAxig1* coding region, a polynucleotide which selectively hybridizes to said polynucleotides under specified stringent conditions, and still having transcriptional regulatory activity. The Examiner further states that the Applicant has not provided guidance for how to obtain all of the polynucleotides of Claims 15 and 16 and use them for the production of transgenic plants with altered fertility. The Examiner states that "[n]o guidance has been provided for any modifications to any of the disclosed sequences...other than ZmAxig1" and that "[n]o regions necessary for auxin-responsive regulatory activity have been disclosed or evaluated for these polynucleotides." (p. 6 of Office Action)

The Applicants respectfully suggest that this rejection was intended to apply to Claims 15 and 21, as Claim 13 has been withdrawn. Applicants also note that references to any isolated polynucleotide having at least 75% sequence identity with SEQ ID NO: 16; to polynucleotides amplified from *Zea mays* nucleic acids library using specified primers; and to nucleic acids from the 5' regulatory region of any polynucleotide having 75% sequence identity to *ZmAxig1* coding region, all still having transcriptional regulatory activity have been removed from Claim 15 and now appear, instead, in new claims 38-52. Claim 15 is now directed to SEQ ID NO: 16 and operable fragments thereof.

The Applicants respectfully traverse the rejection.

It would be unreasonable to require Applicants to detail every permutation of the invention which would function as claimed. The Court stated in *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991): "...we do not imply that patent applicants in art areas currently denominated as 'unpredictable' must never be allowed generic claims encompassing more than the particular species disclosed in their specification. It is well settled that patent applicants are not required to disclose every species encompassed by their claims, even in an unpredictable art..." Indeed, the Examiner states (p. 7 of Office Action), "While Applicant is not required to exemplify each and every claimed embodiment, specific guidance with respect to which region of the disclosed sequences can be modified so that the auxin-responsive regulatory activity is retained is required."

The Applicants respectfully assert that they have in fact provided several points of specific guidance with respect to modification of disclosed sequences. The Examiner acknowledges (see paragraph bridging pages 5 and 6 of the Office Action) that the Applicants provide guidance for isolated promoter sequences from the 5' region of the auxin-induced polynucleotide from Zea mays designated as *ZmAxig1*, and that transformation with a vector (V1 or V2) comprising either of two promoter sequences was effective in providing tissue-preferred, auxin-responsive expression. Thus, the Examiner recognizes that the Applicants have in fact provided enablement for the isolated promoter sequences of vectors V1 and V2 as described in Example 4. This definitively enables two distinct promoter sequences: (a) the .7kb promoter of V1; and (b) the 1.3kb promoter of V2.

Because of the structure and correspondence of the V1 and V2 promoters, efficacy of two additional promoter sequences can be logically inferred, as shown in the attached Figure 1. The promoter of V1 comprises 661 nucleotides, with 5 adenine residues at positions 528 to 532 5' to the start codon. The promoter of V2 comprises 1306 nucleotides, with 4 adenine residues at the corresponding positions. As Example 4 demonstrates, either configuration (5 or 4 adenine residues) and either length (1306 or 661 nucleotides) will function as claimed. Thus, a 1307-base

promoter in which five adenine residues are present at positions 528 to 532 5' to the start codon, and a 660-base promoter in which only four adenine residues are present at the corresponding positions, are enabled. See Figure 1, attached, for a graphic representation. Thus, at a minimum, a complete sequence and three operable fragments are enabled. This information sufficiently enables one of skill in the art to isolate operable fragments of SEQ ID NO: 16.

The Applicants note that the Examiner has cited Kim et al. (Plant Molecular Biology 24:105-117, 1994) and Benfey et al. (Science 250:959-966, 1990) as evidence of the "unpredictability inherent in promoters to function either consitutively or tissue-specifically when one or more nucleotide bases of the promoter are modified." Applicants respectfully submit that the references do not adequately reflect the state of the art as of the priority filing date of July 13, 2000. Applicants acknowledge, as the Examiner points out, that one- or two-nucleotide changes may affect promoter function. However, Applicants strenuously assert that any person of skill in the art is also well aware of that possibility and will conduct tests to evaluate putative operable fragments. In support of this assertion, Applicants note that a search of the Biological Abstracts database *prior to 1995* retrieves over 400 references in which promoter fragments are analyzed for their effect on expression of a linked gene. A similar search, but covering the time frame through 1999, retrieves approximately 100 additional references. This indicates that the techniques for analysis of promoter fragments had been well established and were becoming routine, such that the number of publications reporting such work declined. Thus, a person of skill in the art at the time the application was filed would be able to determine functional fragments, if desired, by using techniques well-known in the art such as, for example, deletion analysis or systematic substitution, followed by appropriate expression assays. Such person would also recognize that certain highly-conserved promoter regions, such as CAAT and TATA elements, are necessary for promoter function, another issue raised by the Examiner on page 7.

Sufficient support for deletion analysis and directed mutagenesis is provided in the specification on page 21, second paragraph. It is well established that "[a] patent need not teach, and preferably omits, what is well known in the art." Spectra-Physics, Inc. v. Coherent, Inc., 827 F.2d 1524, 3 USPQ2d 1737 (Fed. Cir. 1987), *cert. Denied*, 484 U.S. 954 (1987). Further, "[e]nablement is determined from the viewpoint of persons of skill in the field of the invention at the time the patent application was filed." *Ajinomoto Co., Inc., v. Archer-Daniels-Midland Co.*, 228 F.3d 1338, 56 USPQ2d 1332 (Fed. Cir. 2000)

Thus, determination of which fragments meet the conditions of the claims (i.e. a transcriptional regulatory element responsive to the presence of auxin) is a matter of routine experimentation well within the scope allowed by law. See *In re Wands*, 858 F2d 731, 737 (Fed. Cir. 1988), where the court reversed the Board of Patent Appeals and Interferences for holding a biotechnology application not enabled under §112, first paragraph, allegedly because obtaining the claimed subject matter required screening a vast number of cells lacking the claimed function. The *Wands* Court also noted that practitioners in the art routinely engage in such testing. Clearly, even considerable testing is permitted so long as it is routine, as is the case here.

The Applicants acknowledge that while certain fragments may be inoperable, it is well within the realm of reasonable experimentation for a person of skill in the art to generate promoter fragments and determine which are operable. It is well established that "[e]ven if some of the claimed combinations [are] inoperative, the claims are not necessarily invalid. 'It is not a function of the claims to specifically exclude...possible inoperative substances...' *In re Dinh-Nguyen*, 492 F.2d 856, 858-59, 181 USPQ 46, 48 (CCPA 1974) (emphasis omitted)."

Applicants respectfully assert that the social contract of patents requires full disclosure of the invention in return for a right to exclude others from making, using, or selling such invention. In this case the Applicants hav fulfilled their obligation by disclosing the nucleotide sequence of the complete ZmAxig1 promoter region. If

Patent and Trademark Office policy were to allow Applicants patent protection only as to the exact sequence submitted, patentees would be unfairly disadvantaged in that a potential infringer could easily make and test sequence modifications to derive functional fragments and thereby readily circumvent the patent.

The combination of disclosure (i.e., a specific, full-length sequence as a starting point) and level of skill in the art (as indicated by references describing directed mutagenesis and deletion analysis) must be considered in determining whether the invention is enabled.

This enablement rejection is also directed to "transgenic plants and seeds comprising said polynucleotides, and a method of altering plant gene expression or disrupting plant fertility by expressing said polynucleotides in transgenic plants."

Applicants respectfully respond that methods of creating transgenic plants and seeds are fully enabled by Examples 12-14 and the cited references. Methods of altering gene expression or modifying plant fertility are fully enabled by Examples 4 and 7 and the cited references, as read by a person of skill in the art.

In view of the amendments and arguments presented, the Applicants ask that the rejections for enablement under 35 USC 112, first paragraph, be withdrawn.

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Claim Rejections – 35 USC § 112, First Paragraph, Written Description

The Examiner has rejected Claims 15-32 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The Examiner cites *University of California v. Eli Lilly and Co.*, 43 USPQ2d 1398 (Fed. Cir. 1997) (hereinafter "*Lilly*") and the Written Description Examination Guidelines published in the Federal Register, Vol 66, No. 4, Friday, January 5, 2001 (hereinafter "Guidelines").

The Applicants respectfully traverse the rejection.

The Examiner states that "Applicant has not described a single variant having the claimed structural characteristics that retains the desired regulatory activity."

Applicants respectfully state that in fact two specific promoter sequences have been precisely described, the .7kb promoter of V1 and the 1.3kb promoter of V2; and, as explained above and as graphically represented in Figure 1, two additional promoter sequences can be logically inferred.

The Examiner also states that "Applicant has not described the auxin responsive regulatory elements in the disclosed sequences."

Applicants respectfully state that "The test for determining compliance with the written description requirement is whether the disclosure of the application as originally filed reasonably conveys to the artisan that the inventor had possession at that time of the later claimed subject matter, rather than the presence or absence of literal support in the specification for the claim language." *In re Kaslow*, 707 F.2d 1366, 217 USPQ 1089 (Fed. Cir. 1983) Further, "...one skilled in the art, following the teaching of the prior application must be able to produce the subject matter of the later claims." Ralston Purina Co. v. Far-Mar-Co., Inc., 772 F.2d 1570, 227 USPQ 177 (Fed. Cir. 1985). At page 21, second paragraph, the application

provides support for deletion analysis and directed mutagenesis, which the skilled artisan would use in determining auxin-responsive regulatory elements.

While the written description and enablement requirements are distinct, they are entwined. (Guidelines, p. 1100) "The written description must communicate that which is needed to enable the skilled artisan to make and use the claimed invention." Kennecott Corp. v. Kyocera International, Inc., 835 F.2d 1419, 5 USPQ2d 1194 (Fed. Cir. 1987), *cert. denied*, 486 U.S. 1008 (1988). As the Federal Circuit has held (*Union Oil Co. v. Atlantic Richfield Co.*, 208 F.3d 989, 997, 54 USPQ2d 1227, 1232 (Fed. Cir. 2000), "The written description requirement does not require the applicant 'to describe exactly the subject matter claimed, [instead] the description must clearly allow *persons of ordinary skill in the art* to recognize that [he or she] invented what is claimed.' Thus, Section 112, Paragraph 1, ensures that, as of the filing date, the inventor conveyed with reasonable clarity to *those of skill in the art* that he was in possession of the subject matter of the claims." (citations omitted, emphasis added). (Guidelines, p. 1103)

Applicants maintain that in providing the complete nucleotide sequence of the ZmAxig1 promoter region, they have clearly communicated that which is needed for the skilled artisan to make and use the claimed invention.

The Applicants note the reminder in the Guidelines (p. 1100) that "there is a 'strong presumption' that an adequate written description of the claimed invention is present when the application is filed, consistent with *In re Wertheim*, 541 F.2d 257, 263, 191 USPQ 90, 97 (CCPA 1976)."

Further, the Guidelines provide, at p. 1106: "Factors to be considered in determining whether there is sufficient evidence of possession include the level of skill and knowledge in the art, partial structure, physical and/or chemical properties, functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the method of making the claimed invention. Disclosure of any combination of such identifying characteristics that distinguish the claimed invention from other materials and would lead one of skill in the art to the

conclusion that the applicant was in possession of the claimed species is sufficient." (emphasis added)

In the present case the Applicants have provided both complete and partial structures of the ZmAxig1 transcriptional regulatory element (e.g. SEQ ID NO:3, 4, and 16); physical and/or chemical properties (e.g. capable of hybridization under specified conditions; products of amplification using specific primers); functional characteristics alone (e.g. tissue-preferred nature, auxin-responsiveness) or coupled with a known or disclosed correlation between structure and function (e.g. attached Figure 1), and the method of making the claimed invention (e.g. Examples 1-5). Various combinations of these disclosed characteristics are sufficient to lead one of skill in the art to conclude that the Applicants were in possession of the invention as claimed.

The Guidelines state (p. 1104) that "[t]o satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail that one *skilled in the art* can reasonably conclude that the inventor had possession of the claimed invention." (emphasis added)

The Guidelines further provide, p. 1106: "Patents and printed publications in the art should be relied upon to determine whether an art is mature and *what the level of knowledge and skill is in the art.*" (emphasis added)

Determining the level of skill and knowledge in the art is therefore an important factor in determining whether the applicant was in possession of the claimed invention at the time of filing. A search of patents reveals that an application filed May 14, 1989, which issued to Benfey on May 5, 1992, as U.S. patent 5,110,732, (see also Benfey and Chua Science 250:959-966, 1990, as cited by the Examiner) disclosed fragments of the CaMV35S promoter which would selectively direct expression in root and radicle tissue, or in non-root tissue. Thus, the concept that portions of the promoter region influence expression patterns of linked gen s, and knowledg of the techniques to isolate and define such fragm nts, have b en a part of the art since th early 1990s, i.e. 10 years before the

filing date of the present application. The rate of progress in the biotechnological arts is high, as indicated by the search of publications described above. The Applicants would be glad to supply a list of published reports of promoter fragment analysis as of the time the application was filed, if the Examiner so desires.

Applicants further note that the determination of sufficiency of written description is made on a case-by-case basis. *In re Wilder*, 736 F.2d 1516, 222 USPQ 369 (Fed. Cir. 1984) While the Examiner cites *Lilly*, that case concerned the attempt to *extrapolate* from a sequence isolated from one biological species (i.e. rat) to a broad range of sequences which encoded a similar protein in widely-divergent species (i.e., all vertebrates and all mammals). In contrast, in the present case, the *outer range* of the claimed invention is well defined by the specific sequence, SEQ ID NO: 16. Functional variations are circumscribed by the structure of the disclosed sequence. The claims at issue involve a subset of sequences ultimately defined by SEQ ID NO: 16. By possessing the disclosed SEQ ID NO: 16, the inventor, a person of skill in the art, also possessed, at the time of filing the application, all of the variations claimed.

In addition, the present case is distinguished from *Lilly* in that the claimed sequence is a promoter, not a coding sequence, and thus does not fall within guidelines for "a description of a genus of cDNAs."

Further, in *Lilly*, the Court ruled that a chemical compound's name does not necessarily convey a written description of the named chemical compound, particularly when a genus of compounds is claimed, and that the name, *if it does no more than distinguish the claimed genus from all others by function*, does not satisfy the written description requirement because "it does not define any structural features commonly possessed by members of the genus that distinguish them from others." (p. 1406; emphasis added) In contrast, the present case is not relying on a name alone to satisfy the written description requirement, but on a combination of structural disclosure (i.e. the complete promoter sequence) and the level of skill in the art to determine whether a given variant functions as claimed.

The Guidelines further state (page 1101) that "[a]ctual reduction to practice may be crucial *in the relatively rare instances* where the level of knowledge and level of skill are such that those of skill in the art cannot describe a composition structurally, or specify a process of making a composition by naming components and combining steps, in such a way as to distinguish the composition with particularity from all others." (emphasis added)

Further, Applicants note that one comment included in the Federal Register Notice of January 5, 2001, p. 1101, "stated that the written description of a claimed DNA should be required to include the complete sequence of the DNA and claims should be limited to the DNA sequence disclosed." The Office stated, in response, "Describing the complete chemical structure, *i.e.*, the DNA sequence, of a claimed DNA is one method of satisfying the written description requirement, but it is not the only method. *See Eli Lilly*, 119 F.3d at 1566, 43 USPQ2d at 1404 ("An adequate written description of a DNA * * * requires a precise definition, *such as* by structure, formula, chemical name, or physical properties. (emphasis added, internal quote omitted)). Therefore, there is no basis for a *per se* rule requiring disclosure of complete DNA sequences or limiting DNA claims to only the sequence disclosed." (emphasis added)

In view of the level of skill in the art and the substantial disclosure by the Applicants, the written description requirement as established by statute and judicial opinion has been fully met, and the rejections under 35 USC 112, first paragraph should be withdrawn.

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Claim Rejections – 35 USC § 102, Anticipation

Claims 15, 17-22, 25-28 and 30-32 stand rejected by the Examiner under 35 USC 102(b) as being anticipated by Cigan et al. (US 5,795,753, filed June 1995). The Examiner states that "[g]iven the broad interpretations of 'operable fragments', the 5126 gene promoter from maize would inherently comprise an operable fragment of Applicant's SEQ ID NO: 16. Therefore, Cigan teaches all claim limitations."

A proper rejection under 35 USC 102(b) requires that the claimed invention be patented or described in a printed publication. "A prior art reference anticipates a claim only if the reference discloses, either expressly or inherently, every limitation of the claim." *Rowe v. Dror*, 112 F.3d 473, 42 USPQ2d 1550 (Fed. Cir. 1997).

U.S. 5,795,753 discloses the anther- or tapetum-specific promoter 5126 and claims methods of its use in manipulating plant fertility.

Applicants traverse the rejection and respectfully assert that the claims of the current case do not read on the 5126 promoter disclosed in U.S. 5,795,753, and thus there is no anticipation.

The auxin-responsive nature of the ZmAxig1 promoter is not characteristic of the 5126 promoter; hence Claims 15, 17-22, 25-28, 30-32, and new claims 37-52 are not anticipated.

Further, the stringent hybridization conditions of Claim 16, and the percent identity requirements of Claims 40-42, do not describe a sequence reading upon the 5126 promoter, which has an identity to SEQ ID NO: 16 of only 37% using GAP. A BESTFIT analysis of the 5126 and ZmAxig1 promoters shows 62% identity over a single 47-bp segment.

Applicants ask that the rejection under 35 U.S.C. 102(b) be withdrawn.

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CONCLUSION

Applicants believe that all claims under consideration are in condition for allowance, and such action is respectfully requested.

Respectfully submitted,

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